News & Views

Research Highlights

Highlights from the latest articles in acute coronary syndromes

Invasive management of acute coronary syndromes: should we adopt a primary angioplasty strategy for all patients?

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Evaluation of: Montalescot G, Cayla G, Collet JP *et al.*; the ABOARD Investigators: ABOARD: immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. *JAMA* 302, 947–954 (2009).

For patients presenting with moderate- or high-risk non-ST-elevation acute coronary syndromes (NSTE-ACS), an early invasive strategy geared towards revascularization is a class IA indication according to American and European management guidelines. However, the precise timing of coronary angiography has not been completely determined. Montalescot *et al.* sought to clarify this issue in the Angioplasty to Blunt Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD) study.

Patients with at least moderate-risk NSTE-ACS (Thrombolysis in Myocardial Infarction [TIMI] risk score ≥3) were randomly assigned to immediate angiography and revascularization ('primary percutaneous coronary intervention [PCI] model') or to angiography on the next day. The primary end point was peak troponin I during hospitalization and secondary end points included all-cause death, new myocardial infarction (MI; based on creatine kinase-MB rise), urgent revascularization or recurrent ischemia within 1 month. With 352 patients enrolled, the study had 80% power to detect a difference of 0.3 ng/ml in peak troponin I. Baseline characteristics were not different between the 'immediate' (n = 175) and 'delayed' (n = 177) groups. The delay to angiography was 70 min in the immediate group and 20.5 h in the delayed group. PCI was performed in 80 and 70% of the two groups, respectively, and coronary artery bypass graft (CABG) was chosen in 11% in each group. Median peak troponin I, the primary end point, was 2.1 and 1.7 ng/ml, respectively ($p = 0.70$). There were no differences in troponin release according to age, gender, TIMI score or presence of diabetes. There were no significant differences in any of the secondary efficacy end points or bleeding complications between the groups. The length of stay was considerably shorter for the immediate group (55 h) than for the delayed group (77 h; $p < 0.001$).

"In patients with moderate- to high-risk NSTE-ACS, a strategy of immediate intervention compared with a strategy of intervention deferred to the next working day (mean: 21 h) did not result in a difference in MI as defined by peak troponin level."

In this study of 'very early' versus 'early' invasive evaluation for ACS, all patients had excellent adjunctive medical management and high rates of revascularization. The 'primary PCI' approach to NSTE-ACS did not reduce ischemic or hemorrhagic complications compared with a more logistically sound paradigm of angiography on the next day. The reduction in length of stay may be economically important, but would even further reduce the ability to initiate appropriate risk factor modification in an already shortened hospital encounter.

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"There were no significant differences in any of the secondary efficacy end points or bleeding complications between the groups."

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Invasive management of acute coronary syndromes: how early should it occur?

Evaluation of: Mehta SR, Granger CB, Boden WE *et al.*; the TIMACS Investigators: TIMACS: Timing of Intervention in Acute Coronary Syndromes. *N. Engl. J. Med.* 360, 2165–2175 (2009).

Randomized clinical trials and meta-analyses have demonstrated that an early invasive strategy consisting of coronary angiography and revascularization, when appropriate and feasible, is superior to a conservative strategy in patients with NSTE-ACS. The timing of coronary angiography has varied among trials and there is no consensus regarding when it should be undertaken.

The Timing of Intervention in Acute Coronary Syndromes (TIMACS) investigators randomized 3031 patients with moderate- or high-risk NSTE-ACS to an early invasive (<24 h from admission) or a delayed invasive (>36 h) strategy with the goal of establishing the optimal timing of coronary angiography. Crossover from the delayed to the early group was possible in the presence of refractory ischemia, new MI or hemodynamic instability. The primary end point was the composite of all-cause death, new MI or stroke at 6 months. All patients received standard ACS therapy including early loading with clopidogrel. The study had 80% power to detect a 28% reduction in the primary end point.

A quarter of patients in the delayed group crossed over to early angiography and 12% of those randomized to early angiography were studied later than 24 h. The median time to angiography was 14 and 50 h, respectively. All important baseline characteristics were well matched between the two groups. Nearly 80% of all patients had either ischemic ST-T changes or elevated biomarkers on admission. The primary end point occurred in 9.6% of the early group and in 11.3% of the delayed group (p = 0.15). The secondary end point of death, MI or refractory ischemia was reduced in the early group by 28% (9.5 vs 12.9%; p = 0.002). Prespecified analyses according to age, gender, ST deviation, biomarker elevation and Global Registry of Acute Coronary Events (GRACE) risk score demonstrated that the early intervention improved outcome in the third of patients with a GRACE score of more than 140 (14.1 vs 21.6%; p_{int} = 0.01). There was no difference in bleeding complications.

"Prespecified analyses according to age, gender, ST deviation, biomarker elevation and Global Registry of Acute Coronary Events risk score demonstrated that the early intervention improved outcome..."

"In summary, our study showed that in most patients with acute coronary syndromes without ST-segment elevation, an early-intervention strategy did not differ from a delayed-intervention strategy in preventing a composite outcome of death, myocardial infarction or stroke. However, early intervention significantly reduced the risk of refractory ischemia and appeared to be superior to a delayed strategy in high-risk patients."

This is a very well-executed trial demonstrating, together with ABOARD (see previous section) that NSTE-ACS patients initially stabilized medically can be managed with an invasive strategy at any time during the first 48 h without an increase in ischemic or hemorrhagic complications. An important contribution of TIMACS is the observation that high-risk patients (a third of those enrolled) benefit from earlier angiography.

"This is a very well executed trial demonstrating ... that non-ST-elevation acute coronary syndrome patients initially stabilized medically can be managed with an invasive strategy at any time during the first 48 h without an increase in ischemic or hemorrhagic complications."

More potent platelet inhibition prevents ischemic events in acute coronary syndromes

Evaluation of: Wallentin L, Becker RC, Budaj A *et al.*; the PLATO Investigators: PLATO: ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 361, 1045–1057 (2009).

Dual antiplatelet therapy with aspirin (clopidogrel) is recommended for up to 1 year in patients with ACS, with or without ST-segment elevation. Clopidogrel has unpredictable and slow metabolism to its active metabolite and only modest and varying platelet inhibition. The Platelet Inhibition and Patient Outcome Trial (PLATO) Investigators randomized 18,624 patients with ACS to clopidogrel (loading dose of 300–600 mg and daily dose of 75 mg) or to ticagrelor, a novel reversible, oral direct inhibitor of the $P2Y_{12}$ receptor (loading dose of 180 mg and twice-daily dose of 90 mg). The primary end points were the combination of cardiovascular death, MI or stroke (efficacy) and major bleeding (safety) at 1 year. The study had 90% power to detect a 13.5% risk reduction with ticagrelor.

"The primary efficacy end point occurred significantly less often in ticagrelor-treated patients than in clopidogrel-treated patients (9.8 vs 11.7%; p < 0.001)."

The two groups were well balanced with respect to baseline characteristics and clinical presentation (38% had ST-elevation MI). Coronary angiography, PCI and CABG were performed in 81, 61 and 4% of each group, respectively. The primary efficacy end point occurred significantly less often in ticagrelor-treated patients than in clopidogrel-treated patients (9.8 vs 11.7%; $p < 0.001$) and MI, CV death and all-cause death were individually significantly reduced by ticagrelor. Major bleeding was similar between the two groups, although non-CABG major bleeding was more common with ticagrelor (4.5 vs 3.8%; $p = 0.03$). Definite or probable stent thrombosis was reduced by ticagrelor by 25% ($p = 0.02$). Dyspnea was more common in the ticagrelor group (13.8 vs 7.8%; $p < 0.001$) but only 0.9% of patients discontinued use because of it.

"...in patients who had an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor, as compared with clopidogrel, significantly reduced the rate of death from vascular causes, myocardial infarction or stroke."

The benefit of ticagrelor was independent of clopidogrel loading dose, use of invasive therapy or type of ACS.

"…in patients who had an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor, as compared with clopidogrel, significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke, without an increase in the rate of overall major bleeding but with an increase in the rate of nonprocedure-related bleeding."

The PLATO trial extends the evidence that more powerful platelet inhibition in ACS patients is associated with clinically-relevant reductions in ischemic events, both immediately and up to 1 year. Like with clopidogrel, the benefit extends in patients treated with medical therapy alone and in those receiving revascularization, without a significant increase in major bleeding.

The intricacies of dual antiplatelet therapy

Evaluation of: Mehta SR; the CURRENT Investigators: CURRENT – OASIS 7: A 2 x 2 factorial randomized trial of optimal clopidogrel and aspirin dosing in patients with ACS undergoing an early invasive strategy with intent for PCI. Presented at: *European Society of Cardiology Annual Meeting, 2009.* Madrid, Spain, 29 August–2 September 2009.

The optimal dosing of aspirin in patients with vascular disease has not been studied prospectively. Meta-analyses suggest that low doses are as effective as higher doses, but have fewer hemorrhagic complications. Similarly, loading doses of clopidogrel of 300 and 600 mg and maintenance doses of 75 and 150 mg have been used but were never compared in a rigorous study. European and American guidelines differ in their recommendations on these issues. Patients with acute coronary syndromes (with or without ST-elevation) with planned early (<24 h) angiography and PCI were randomized to clopidogrel 600 mg followed by 150 mg daily for 1 week and then 75 mg, or 300 mg followed by 75 mg daily. A second randomization was performed to aspirin 300–325 mg or 75–100 mg daily. The primary end points were CV death, MI or stroke at 30 days (efficacy), stent thrombosis at 30 days and major bleeding (safety). Of 25,087 patients enrolled, 80% had ischemic ECG changes and 42% had elevated biomarkers. NSTE-ACS was present in 71%, while 29% had STEMI. Angiography was performed per protocol in 99% of patients, leading to PCI in 70%, CABG in 7.3% and medical management alone in 22%. One in seven patients did not have significant CAD.

For the aspirin comparison, there was no significant difference in the primary efficacy (4.4 vs 4.2%) and safety (2.3 vs 2.3%) end points between the low and high doses, respectively. PCI and no-PCI patients also had very similar rates of events. There was borderline more GI bleeding in the higher aspirin dose (0.38 vs 0.24%; p = 0.051).

The results of the clopidogrel comparison were more nuanced. There was significant statistical interaction between the clopidogrel dose and aspirin dose (p = 0.043) and between clopidogrel dose and performance of PCI (p = 0.016). Overall, the composite of CV death, MI or stroke was similar in patients receiving standard- or double-dose clopidogrel (4.4 vs 4.2%). However, in the PCI patients, the double dose reduced events by 15%, from 4.5 to 3.9% (p = 0.036). Most of the difference was in fewer MI events. Double-dose clopidogrel reduced definite stent thrombosis at 30 days by 42% (p = 0.001). Among recipients of high-dose aspirin, double-dose clopidogrel reduced events by 17%, but this effect was not noted in the low-dose aspirin group. CURRENT severe bleeding and blood transfusions were significantly more common in the double-dose group, regardless of aspirin dose.

"...double-dose clopidogrel loading and maintenance (for 1 week) is significantly more efficacious than standard dose in patients undergoing PCI within 24 h of admission."

Thus, this important, large ACS trial demonstrated that double-dose clopidogrel loading and maintenance (for 1 week) is significantly more efficacious than standard dose in patients undergoing PCI within 24 h of admission, with minimal excess bleeding (only using the CURRENT scale). Aspirin dose did not affect efficacy or safety.

These results, together with those of PLATO (ticagrelor) and Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38; prasugrel) will undoubtedly influence the paradigm of care for ACS.